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Oxidative stress regulated genes in nigral dopaminergic neuronal cells: correlation with the known pathology in Parkinson's disease.

Yoo MS, Chun HS, Son JJ, DeGiorgio LA, Kim DJ, Peng C, Son JH.

Laboratory of Molecular Neurobiology, Department of Neurology and Neuroscience, Weill Medical College of Cornell University at the W.M. Burke Medical Research Institute, 785 Mamaroneck Ave., White Plains, NY 10605, USA.

Oxidative stress (OS) is a primary pathogenic mechanism of nigral dopaminergic (DA) cell death in Parkinson's disease (PD). Oxidative damage, Lewy body formation and decreased mitochondrial complex I activity are the consistent pathological findings in PD. In nigral DA neurons, however, it is unknown whether any gene expressional changes induced by OS contribute to the typical PD pathology. Here, using microarray analysis, we identified several groups of genes in the nigral DA cell line, SN4741 [J. Neurosci. 19 (1999) 10; J. Neurochem. 76 (2001) 1010], that were regulated by OS. Approximately 36 significantly regulated genes that encode functional molecules of nuclear subunits of mitochondrial complex I, exocytosis and membrane trafficking proteins, markers for OS and oxidoreductases, regulatory molecules of apoptosis and unidentified EST clones were further analysed. OS modulated the expression of specific genes, of which physiological dysfunctions have been implicated in PD. For instance, the expression of the nuclear-encoded subunits of mitochondrial complex I, B8 and B17, were significantly down-regulated by OS, possibly contributing to selective defect in mitochondrial complex I activity in PD. Furthermore, syntaxin 8 and heme oxygenase-1 (HO-1) are most dramatically up-regulated by OS in DA cells. Syntaxin 8 is a SNARE protein, regulating lipid vesicle docking and fusion as well as early endosome membrane recycling. Lipid membranes are significantly oxidative-damaged in PD. HO-1 is an important cytoplasmic constituent of Lewy bodies, a pathological hallmark of idiopathic PD. Thus, our findings provide novel molecular probes that may be useful in unraveling the molecular mechanism(s) of OS-induced pathogenesis in PD. Further functional characterization of the affected genes including ESTs can help elucidate the underlying molecular pathology as well as develop biomarkers for monitoring degenerating DA neurons in PD.

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